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Ng O, Keeler BD, Mishra A, Simpson JA, Neal K, Al-Hassi HO, Brookes MJ, Acheson AG

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Iron therapy for preoperative anaemia (Review)

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[Intervention Review]

Iron therapy for preoperative anaemia

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ABSTRACT

Background

Preoperative anaemia is common and occurs in 5% to 76% of patients preoperatively. It is associated with an increased risk of perioperative allogeneic blood transfusion, longer hospital stay, and increased morbidity and mortality. Iron deficiency is one of the most common causes of anaemia. Oral and intravenous iron therapy can be used to treat anaemia. Parenteral iron preparations have been shown to be more effective in conditions such as inflammatory bowel disease, chronic heart failure and postpartum haemorrhage due to rapid correction of iron stores. A limited number of studies has investigated iron therapy for the treatment of preoperative anaemia. The aim of this Cochrane Review is to summarise the evidence for iron supplementation, both enteral and parenteral, for the management of preoperative anaemia.

Objectives

To evaluate the effects of preoperative iron therapy (enteral or parenteral) in reducing the need for allogeneic blood transfusions in anaemic patients undergoing surgery.

Search methods

We ran the search on 30 July 2018. We searched the Cochrane Injuries Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library), Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R), Embase Classic and Embase (Ovid), CINAHL Plus (EBSCO), PubMed, and clinical trials registries, and we screened reference lists. We ran a top-up search on 28 November 2019; one study is now awaiting classification.

Selection criteria

We included all randomised controlled trials (RCTs) that compared preoperative iron monotherapy to placebo, no treatment, standard care or another form of iron therapy for anaemic adults undergoing surgery. We defined anaemia as haemoglobin values less than 13 g/dL for males and 12 g/dL for non-pregnant females.

Data collection and analysis

Two review authors collected data and a third review author checked all collected data. Data were collected on the proportion of patients who receive a blood transfusion, the amount of blood transfused per patient (units), quality of life, ferritin levels and haemoglobin levels, measured as continuous variables at the following predetermined time points: pretreatment (baseline), preoperatively but postintervention, and postoperatively. We performed statistical analysis using the Cochrane software, Review Manager 5. We summarised outcome data in tables and forest plots. We used the GRADE approach to describe the quality of the body of evidence.

Main results

Six RCTs, with a total of 372 participants, evaluated preoperative iron therapy to correct anaemia before planned surgery. Four studies compared iron therapy (either oral (one study) or intravenous (three studies)) with no treatment, placebo or usual care, and two studies compared intravenous iron therapy with oral iron therapy. Iron therapy was delivered over a range of periods that varied from 48 hours to three weeks prior to surgery. The 372 participants in our analysis fall far short of the 819 required - as calculated by our information size calculation - to detect a 30% reduction in blood transfusions. Five trials, involving 310 people, reported the proportion of participants who received allogeneic blood transfusions.

Meta-analysis of iron therapy versus placebo or standard care showed no difference in the proportion of participants who received a blood transfusion (risk ratio (RR) 1.21, 95% confidence interval (CI) 0.87 to 1.70; 4 studies, 200 participants; moderate-quality evidence). Only one study that compared oral versus intravenous iron therapy measured this outcome, and reported no difference in risk of transfusion between groups.

There was no difference between the iron therapy and placebo/standard care groups for haemoglobin level preoperatively at the end of the intervention (mean difference (MD) 0.63 g/dL, 95% CI -0.07 to 1.34; 2 studies, 83 participants; low-quality evidence). However, intravenous iron therapy produced an increase in preoperative postintervention haemoglobin levels compared with oral iron (MD 1.23 g/dL, 95% CI 0.80 to 1.65; 2 studies, 172 participants; low-quality evidence). Ferritin levels were increased by intravenous iron, both when compared to standard care ((MD 149.00, 95% CI 25.84 to 272.16; 1 study, 63 participants; low-quality evidence) or to oral iron (MD 395.03 ng/mL, 95% CI 227.72 to 562.35; 2 studies, 151 participants; low-quality evidence).

Not all studies measured quality of life, short-term mortality or postoperative morbidity. Some measured the outcomes, but did not report the data, and the studies which did report the data were underpowered. Therefore, uncertainty remains regarding these outcomes. The inclusion of new research in the future is very likely to change these results.

Authors' conclusions

The use of iron therapy for preoperative anaemia does not show a clinically significant reduction in the proportion of trial participants who received an allogeneic blood transfusion compared to no iron therapy. Results for intravenous iron are consistent with a greater increase in haemoglobin and ferritin when compared to oral iron, but do not provide reliable evidence. These conclusions are drawn from six studies, three of which included very small numbers of participants. Further, well-designed, adequately powered, RCTs are required to determine the true effectiveness of iron therapy for preoperative anaemia. Two studies are currently in progress, and will include 1500 randomised participants.

PLAIN LANGUAGE SUMMARY

Iron treatment for low red blood cell count prior to surgery

Review question: we reviewed the evidence for giving iron treatment to people with a low red blood cell count (anaemia) before they had major surgery, to see if it reduced their need for blood transfusions around the time of surgery. We found six studies that looked at this question.

Background: anaemia is a common problem for people about to have surgery. Anaemia can cause dizziness, shortness of breath and lack of energy, as well as increase the risks of surgery and of blood transfusion. Anaemia is commonly due to lack of iron, and iron treatment - with tablets or injections - has been shown to be effective in other situations for treating anaemia. Limited research has looked at whether iron treatment works before surgery.

Search date: on 30 July 2018 we conducted a wide ranging search of the medical literature to identify relevant medical studies.

Study characteristics: we looked at adults with anaemia who were due to have an operation, who received iron treatment or usual care, or a 'pretend' iron treatment (placebo) prior to their surgery. We also compared different forms of iron therapy with each other. We included six studies and a total of 372 participants.

Key results: iron treatment did not reduce the risk of blood transfusion. There is currently insufficient evidence to say whether iron therapy given before surgery prevents transfusions. To date, too few studies involving too small a number of people have been undertaken, and it is not yet possible to obtain a reliable result for the effects of this treatment.

Quality of evidence: the major limitation in study design for all trials was the small size of the sample groups. More research in larger, well-designed trials is needed before a definitive answer can be given about whether iron therapy before surgery is helpful. The Cochrane Review authors judged that five of the six studies included in this review were at a low risk of bias (and so their results are likely to be reliable). This was despite a lack of blinding of participants in five of the trials (which would usually decrease the reliability of the evidence), as the measurement used to assess how well the therapy had worked (blood haemoglobin level) was unlikely to be influenced by the participant or investigator knowing which treatment had been received. The results of one study are at a high risk of bias because participants who did not take 80% of their assigned treatment were not included in the analysis.

Overall the quality of evidence is low (according to the GRADE criteria). When additional research becomes available in the future, it is likely to change the results obtained in this review.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Iron therapy compared to placebo, no treatment or standard care for preoperative anaemia

Iron therapy compared to placebo, no treatment or standard care for preoperative anaemia

Patient or population: people with preoperative anaemia awaiting major surgery

Settings: hospital

Intervention: iron therapy

Comparison: placebo, no treatment or standard care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo, no treatment or standard care	Iron therapy				
Proportion of participants who received a blood transfusion	438 per 1000	386 per 1000 (307 to 482)	RR 1.21 (0.87 to 1.70)	200 (4 studies)	⊕⊕⊕⊕ Low^a	
Any validated measure of quality of life (measured by SF36)	6 ± 17	8 ± 18	-	72 (1 study)	⊕⊕⊕⊕ Very low^b	
Haemoglobin levels at end of preoperative treatment (g/dL)	The mean haemoglobin level in the control groups was 11.0 g/dL	The mean haemoglobin levels in the intervention groups was 0.63 g/dL higher (0.07 lower to 1.34 higher)	MD 0.63 (-0.07 to 1.34)	83 (2 studies)	⊕⊕⊕⊕ Low^c	
Haemoglobin levels post-treatment and surgery (g/dL)	The mean haemoglobin level in the control groups was 10.2 g/dL	The mean haemoglobin levels in the intervention groups was 0.17 g/dL higher (0.29 lower to 0.63 higher)	MD 0.17 (-0.29 to 0.63)	86 (2 studies)	⊕⊕⊕⊕ Low^c	
Ferritin at the end of pre-operative treatment (ng/mL)	The mean ferritin level in the control group was 99 ng/mL	The mean ferritin level in the intervention groups was 149 ng/mL higher (26 higher to 272 higher)	MD 149.00 (25.68 to 272.32)	76 (1 study)	⊕⊕⊕⊕ Low^c	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SF-36:** Short-Form Survey 36

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded 2 levels for imprecision with only four randomised control trials including subsets of anaemic participants, resulting in a small number of participants.

^bDowngraded 3 levels for imprecision with only one study, with a small number of participants and no blinding.

^cDowngraded 2 levels for imprecision with only one study with a small number of participants available.

Summary of findings 2. Intravenous iron therapy compared to oral iron therapy for preoperative anaemia

Intravenous iron therapy compared to oral iron therapy for preoperative anaemia

Patient or population: people with preoperative anaemia awaiting major surgery

Settings: hospital

Intervention: intravenous iron therapy

Comparison: oral iron therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oral iron therapy	Intravenous iron therapy				
Proportion of participants who received a blood transfusion	No data available	No data available	-	-	-	
Any validated measure of quality of life	No data available	No data available	-	-	-	
Haemoglobin levels at end of preoperative treatment (g/dL)	The mean haemoglobin level in the oral iron groups was 10.3 g/dL	The mean haemoglobin level in the IV iron groups was 1.23 g/dL higher (0.80 to 1.65 higher)	MD 1.23 (0.80 to 1.65)	172 (2 studies)	⊕⊕⊕⊕ Low^a	
Haemoglobin levels post-treatment and surgery (g/dL)	No data available	No data available	-	-	-	

Ferritin preoperatively postintervention (ng/L)	The mean ferritin level in the oral iron groups was 23 ng/mL	The mean ferritin level in the IV iron groups was 395 ng/mL higher (228 higher to 562 higher)	MD 395.03 (227.72 to 562.35)	151 (2 studies)	⊕⊕○○ Low^a
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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **IV:** intravenous; **MD:** mean difference

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^a Downgraded twice overall: 1 level due to risk of bias (attrition bias), as the [Kim 2009](#) study excluded participants with less than 80% compliance with therapy (compliance was lower in the oral group); and 1 level for imprecision as only two studies with a small number of participants contributed to the results.

BACKGROUND

Description of the condition

'Anaemia' is defined as a total reduction in erythrocyte number, a reduced amount of circulating haemoglobin, or a decreased circulating red blood cell mass (Perkins 2006), that results in a pathological state where the oxygen-carrying capacity of blood is insufficient to meet physiological demand (Varat 1972). The World Health Organization (WHO) defines anaemia as a haemoglobin level of less than 12 g/dL in non-pregnant adult women, less than 11 g/dL in pregnant adult women, and less than 13 g/dL in adult men. Anaemia is a common finding in preoperative patients, with a prevalence ranging from 5% to 76% depending on the age of the patient, the nature of the condition, and operation planned (Shander 2004). The most common form of anaemia is caused by iron deficiency, which can occur following excessive losses of blood, such as chronic haemorrhage, or inadequate iron intake (Piednoir 2011).

Anaemia can cause symptoms such as dizziness, shortness of breath, angina and lethargy. Anaemia in a preoperative setting is associated with an increased requirement for perioperative blood transfusion (Benoist 2001). In patients undergoing colorectal surgery, preoperative anaemia is an independent risk factor for postoperative complications and a longer postoperative hospital stay (Leichtle 2011). Other studies have shown that perioperative anaemia is associated with an increased risk of perioperative infection and mortality (Dunne 2002).

Description of the intervention

Oral iron supplementation and allogeneic blood transfusion are the current standard treatments for preoperative anaemia. Preoperative, oral iron supplementation has been investigated in colorectal surgery (Lidder 2007; Quinn 2010), and orthopaedic surgery (Lachance 2011), with mixed results. The treatment is cheap, widely available, and easily administered. However, oral iron is associated with a number of gastrointestinal side effects in up to 52% of recipients, which is 2.6 times more than intravenous iron (Tolkien 2015). These include abdominal pain, constipation, diarrhoea and dyspepsia (Tolkien 2015). Non-compliance as a result of these side effects is a common problem (Tolkien 2015). Oral iron supplementation may also be insufficient to compensate for ongoing blood losses, or low serum iron levels caused by hepcidin-mediated reduced intestinal absorption and storage of iron by macrophages, both of which result from inflammation (Ganz 2003).

Parenteral iron was first introduced in the early 20th century in the form of intramuscular and subcutaneous injections (Heath 1932). However, these early formulations caused severe toxic reactions, which led to their disuse. Towards the latter half of the 20th century, high-molecular-weight iron dextran was introduced for both intravenous and intramuscular use, however, this has since been phased out due to reports of fatal anaphylactic-type reactions caused by the instability of the molecule (Chertow 2004), as well as the formation of antidextran antibodies. It has been replaced with low-molecular-weight iron dextran and other newer formulations of intravenous iron, such as iron sucrose, ferric gluconate, ferumoxytol, ferric carboxymaltose and iron isomaltoside.

There has been major progress in the development of newer formulations of intravenous iron. Previously, iron sucrose, a safer formulation that was not associated with anaphylactic-type reactions, had to be given in maximum doses of 200 mg for each infusion, thus requiring several small-dose infusions to achieve the calculated iron deficit. Newer agents, such as ferric carboxymaltose and iron isomaltoside have now been developed; these allow total dose infusion, have much higher maximum approved doses, and have not been associated with anaphylactic-type reactions (Auerbach 2010).

Most research around the use of intravenous iron has centred on the treatment of anaemia in inflammatory bowel disease and chronic kidney disease. Early studies have shown that intravenous iron is effective for treating anaemia in inflammatory bowel disease, with a quicker result than oral iron and fewer side effects, which is an important factor for ensuring compliance (Kulnigg 2008). The use of intravenous iron in anaemic patients with chronic heart failure has been shown to improve symptoms and quality of life significantly (Anker 2009; Okonko 2008). In women with postpartum iron deficiency anaemia, intravenous iron has been shown to be safe, and at least as effective as oral iron, but with fewer gastrointestinal side effects (Breyman 2008; Seid 2008). Kim 2009 showed that intravenous iron was more effective than oral iron in the treatment of preoperative anaemia in women with menorrhagia. The use of intravenous iron in patients with chronic kidney disease is more effective than oral iron, and has fewer side effects (Qunibi 2011).

However, only a limited number of studies has looked at the use of intravenous iron for anaemia in a preoperative setting, and these have mainly concerned orthopaedic surgery. Some of these studies have shown reduced risks of transfusion and infection with the use of intravenous iron (Cuenca 2004; Garcia-Erce 2005). An observational study in patients undergoing major surgery (colorectal cancer resections, hysterectomies and lower limb arthroplasties) saw an average increase in haemoglobin level of 2 g/dL within a three- to five-week period in patients who received intravenous iron (Munoz 2014).

How the intervention might work

The bone marrow requires an internal iron turnover of 20 mg to 30 mg/day for erythropoiesis (formation of red blood cells). The body absorbs 1 mg to 2 mg/day of dietary iron, despite the normal diet containing 15 mg to 20 mg of iron. Ferrous sulphate is one of the most commonly used oral iron supplements and a 200 mg tablet contains 65 mg iron. Oral iron is absorbed mainly in the duodenum where it is reduced into a ferrous state by the duodenal enterocytes and exported via the iron exporter, ferroportin, into the circulation bound to transferrin (Munoz 2009). Oral iron is absorbed most readily on an empty stomach, however, this also increases the risk of gastrointestinal side effects. Therefore, iron supplements are often taken with food to minimise the side effects, although this may decrease the absorption by 40% to 66% (Swain 1996). Some drugs, such as antacids, proton pump inhibitors and tetracyclines, also reduce iron absorption.

Current intravenous iron preparations consist of iron-carbohydrate complexes. Following intravenous injection, the iron-carbohydrate complex is taken up and phagocytosed by the reticuloendothelial system and the remaining iron core is exported out of the cell and transported for erythropoiesis and storage (Munoz 2009).

New erythrocytes generated following the correction of iron-restricted erythropoiesis in bone marrow have a longer half-life than transfused erythrocytes (Kickler 1985).

The use of intravenous iron bypasses the problems of poor absorption that arise with oral iron supplements. Intravenous iron is also better tolerated, with far fewer gastrointestinal side effects than oral iron (Qunibi 2011). Newer formulations of intravenous iron, such as ferric carboxymaltose, can be given in large doses (up to 1000 mg) and studies have shown that intravenous iron results in a more rapid rise in haemoglobin compared to oral iron supplementation (Qunibi 2011). Intravenous iron is now regarded as safe and efficacious, especially in settings where oral iron is ineffective or inappropriate, such as in the presence of colitis or anaemia of chronic disease from chronic inflammation (Auerbach 2014).

Why it is important to do this review

Preoperative anaemia is a predictor of perioperative allogeneic blood transfusion (Shander 2004). Despite screening of blood products, allogeneic blood transfusion carries risks, such as viral transmission, immunomodulation, allergic reactions and alloimmunisation and increased infection (Vamvakas 2009). It has also been independently associated with increased morbidity and mortality (Ferraris 2012; Glance 2011), and reduced cancer-related survival (Acheson 2012). Studies have also associated preoperative anaemia with increased postoperative morbidity and mortality and increased length of hospital stay (Acheson 2012; Beattie 2009; Gupta 2013; Spahn 2010).

Oral iron is considered as first-line therapy if time and disease biology allow for its use. It is cheap and effective in those that can absorb and tolerate it. When not tolerated, or if surgical intervention is planned imminently, intravenous iron provides a method of management of anaemia that is increasingly used to treat preoperative anaemia. It can be given as a large, single-dose regimen with fewer gastrointestinal side effects than oral iron tablets (Auerbach 2014). It is considerably more expensive than oral iron, and there are no conclusive data to show that it reduces healthcare utilisation, or regarding its cost-effectiveness (Fragoulakis 2012). It is recommended for preoperative anaemia, especially if the proposed surgery is urgent (due in less than six weeks) or where oral iron therapy is not tolerated (Munoz 2017).

The aim of this Cochrane Review is to summarise the evidence for use of iron supplementation, both oral and intravenous, for the management of preoperative anaemia. The evidence from this review will establish if there is justification for a large randomised controlled trial to investigate the use of intravenous iron in preoperative anaemia.

OBJECTIVES

To evaluate the effects of preoperative iron therapy (enteral or parenteral) in reducing the need for allogeneic blood transfusions in anaemic patients undergoing surgery.

METHODS

Criteria for considering studies for this review

Types of studies

In order to be eligible for inclusion in the review, all RCTs taking place after 2010 had to have been prospectively registered (Roberts 2015). All RCTs that published their results prior to 2010 were eligible for inclusion.

We considered all randomised controlled trials (RCTs) that compared preoperative iron monotherapy to placebo, no treatment, standard care or another form of iron therapy. Cross-over studies were eligible for inclusion in the review, though we would use data from the first phase only. Trials that used iron therapy in combination with other interventions were not eligible for inclusion in this review.

Types of participants

Anaemic adults over the age of 18 years undergoing surgery. We have defined anaemia as haemoglobin values less than 13 g/dL for males and less than 12 g/dL for non-pregnant females (as per the WHO standard guidelines). We accepted different criteria for anaemia that were used in studies, if the study investigators provided a clear definition of what they considered constituted anaemia.

We included trials that did not specify anaemic participants, if there was stratification of results to an anaemic subgroup. We did not include pregnant women in this review.

Types of interventions

We included trials that began the administration of iron between the day of decision for surgery and the day before surgery. We included trials with any dose, duration, formulation, or route (enteral or parenteral) of iron therapy.

We compared an iron therapy intervention against placebo, no treatment or standard care (as described in each trial protocol), or between two iron therapy interventions. We excluded trials where the effect of iron was combined with another co-intervention (for example erythropoiesis-stimulating agents).

Types of outcome measures

Primary outcomes

- Proportion of participants who received a blood transfusion

Secondary outcomes

- Amount of blood transfused per participant (units)
- Postoperative mortality in the short term (within 30 days) and long term (from 31 days up to one year)
- Postoperative morbidity (including infection and adverse events within 30 days)
- Any validated measure of quality of life (within 30 days)
- Measurement of the following haematologic parameters: haemoglobin, haematocrit, ferritin level and reticulocyte count, measured as continuous variables at predetermined time points: pretreatment; preoperatively but post-treatment; and postoperatively.

Information size calculation for the primary outcome

Assuming that 20% of participants in the control group will require a blood transfusion, and that there is a treatment effect of 30% (i.e. 14% require transfusion following iron therapy), 819 people need to be randomised to receive either iron therapy or control in order to obtain a reliable estimate of the treatment effect ($\alpha = 0.05$, $\beta = 0.1$) (Keeler 2015).

Search methods for identification of studies

In order to reduce publication and retrieval biases we did not restrict our search by language, date or publication status.

Electronic searches

An updated search was run on 30 July 2018, and the results of this have been fully incorporated into the review:

- Cochrane Injuries Group Specialised Register (30 July 2018);
- Cochrane Central Register of Controlled Trials (CENTRAL; the Cochrane Library Issue 10, 2018);
- Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to 30 July 2018);
- Embase Classic and Embase (Ovid SP) (1947 to 30 July 2018);
- PubMed (30 July 2018);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to 30 July 2018);
- ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 30 July 2018);
- ClinicalTrials.gov (clinicaltrials.gov) (30 July 2018);
- WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch) (30 July 2018).

All 30 July 2018 search strategies are listed in [Appendix 1](#). We adapted the MEDLINE search strategy as necessary for each of the other databases: the added study filter is a modified version of the Ovid MEDLINE Cochrane Highly Sensitive Search Strategy for identifying randomised trials; to the Embase search strategy we added the study design terms as used by the UK Cochrane Centre (Lefebvre 2011).

On 28 November 2019, the Cochrane Injuries Group's Information Specialist ran a top-up search of these databases, the searches are listed in [Appendix 2](#); one study is now awaiting classification.

Searching other resources

We did not search any other resources.

Data collection and analysis

The Cochrane Injuries Group's Information Specialist ran the July 2018 searches and collated the search results before passing them on to two review authors (ON and BK) for screening. The results of the November 2018 top-up searches were given an initial screening by the Information Specialist before being passed to the review authors for further examination.

Selection of studies

Two review authors (ON and BK) examined the citations independently and applied pre-agreed selection criteria to identify all potentially eligible studies. Both review authors reviewed the full text of all randomised trials that used iron therapy in surgery. There were no disagreements between authors. We describe the characteristics of excluded studies and reasons for their exclusion in the '[Characteristics of excluded studies](#)' table.

Data extraction and management

Independently, two review authors (ON and BK) extracted data relevant to each included study using a standardised data extraction form, and presented information about the studies in the '[Characteristics of included studies](#)' table. Both BK and another review author (HA) independently double-checked the data. There were no disagreements between the review authors. BK, ON, JS, MB and AA are authors of one of the included trials, [Keeler 2017](#). AM independently extracted data from [Keeler 2017](#) to avoid bias. In addition, the Cochrane Funding Arbiter's panel recommended that a new, unconflicted review author should repeat the data extraction and assessment of risk of bias. This author, HA, independently checked all data extraction, 'Risk of bias' tables and conclusions, including [Keeler 2017](#), to ensure there was no serious bias in the review findings.

Assessment of risk of bias in included studies

Two review authors (ON and BK) independently assessed each study report for risk of bias by making judgements on the following questions according to the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A third review author (HA) independently assessed risk of bias to ensure agreement.

- Was the allocation sequence adequately generated (to check for possible selection bias)?
- Was the allocation sequence adequately concealed (to check for possible selection bias)?
- Was the study blinded with reference to participants, personnel and outcome assessors (to check for possible performance bias)?
- Was there a suggestion of incomplete outcome data (to check for possible attrition bias through withdrawals, dropouts and protocol deviations)?
- Was there any suggestion of selective outcome reporting?
- Were there any other sources of bias?

We assessed the magnitude and direction of bias based upon our assessment of each study. If we considered bias likely to impact on findings, we planned to explore the effect of the potential bias by undertaking sensitivity analyses, however, this was not possible, due to lack of data.

A summary of our decisions about different domains of bias is shown in [Figure 1](#) and [Figure 2](#).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Six studies are included in this review.

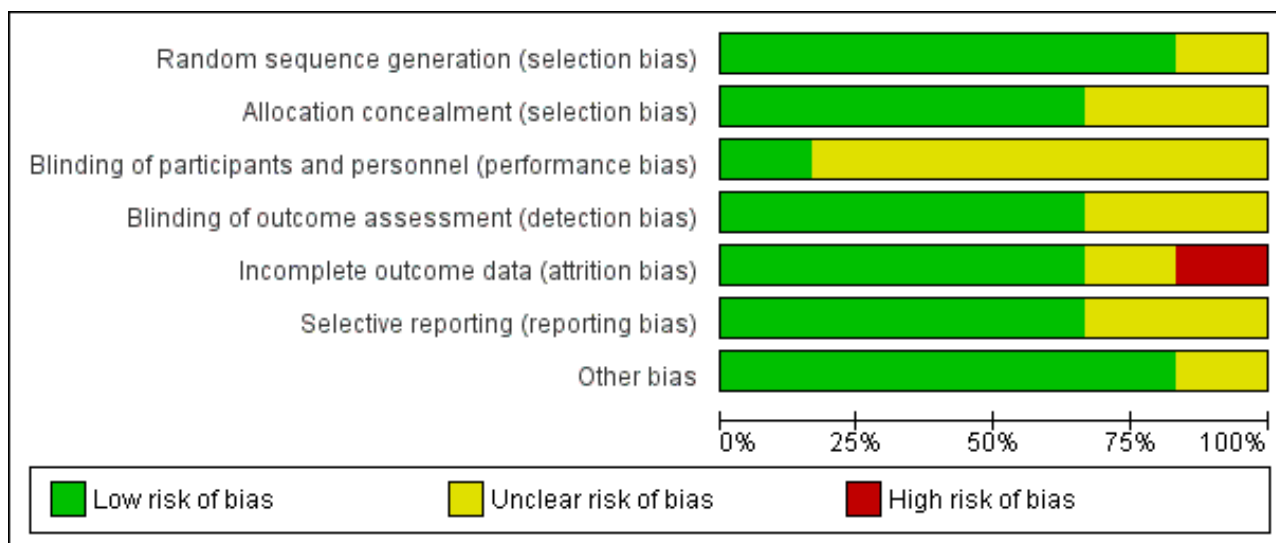


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Edwards 2009	+	+	+	+	+	?	+
Froessler 2016	+	+	?	?	+	+	?
Keeler 2017	+	+	?	+	+	+	+
Kim 2009	+	+	?	?	-	+	+
Lidder 2007	?	?	?	+	?	+	+
Serrano-Trenas 2011	+	?	?	+	+	?	+

Measures of treatment effect

For dichotomous data, we present results as summary risk ratios (RRs) with 95% confidence intervals (CIs).

For continuous data we calculated mean differences (MDs) with 95% CIs between the study groups.

The amount of blood transfused per participant was measured in units (where one unit contains approximately 250 mL of blood).

Unit of analysis issues

The unit of analysis was the participant. For cross-over studies we decided we would include data from the first period before the cross-over only, due to challenges with defining a wash-out period of suitably long duration.

Dealing with missing data

For included studies, we noted the levels of attrition in the 'Risk of bias' tables. We carried out analyses on an intention-to-treat basis

as far as possible. We emailed trial authors for missing data, but received no responses.

Assessment of heterogeneity

We assessed included trials for heterogeneity by examining forest plots visually for estimated treatment effects. We used the I^2 statistic to assess statistical heterogeneity. We regarded heterogeneity as moderate when I^2 was greater than 30%.

Assessment of reporting biases

We assessed included trials for reporting bias based upon the absence of main outcomes expected for trials of iron therapy, namely blood transfusion, and levels of haemoglobin and ferritin. Where practicable, we compared the a priori research protocol with the published report.

Data synthesis

We carried out statistical analysis using the Cochrane software, [Review Manager 2014](#). We used a fixed-effect model in the meta-analysis and the Mantel-Haenszel test for statistical significance.

We present outcome data in tables and as forest plots. We interpreted our findings using the GRADE approach and created 'Summary of findings' tables using GRADE Profiler ([GRADEpro GDT](#)), according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We compared measurements taken at final follow-up between treatment groups.

In the 'Summary of findings' tables, we report the main study outcomes with the data available. These include the number of participants who received a blood transfusion, quality of life, haemoglobin levels at the end of preoperative treatment (g/dL), haemoglobin levels postoperatively (g/dL) and ferritin levels (ng/mL).

Subgroup analysis and investigation of heterogeneity

In future updates of this review, if we identify heterogeneity ($I^2 > 30\%$), we will investigate it using subgroup analysis and sensitivity analysis. We plan to carry out the following subgroup analyses:

- variations in interventions (e.g. dosing, time period of intervention, formulation of iron);
- different types of operations;
- different patient populations;
- different control groups (placebo, no treatment, or standard practices).

Sensitivity analysis

In future updates of this review, if data permit, we will conduct sensitivity analysis based on allocation concealment (low risk of bias versus unclear or high risk of bias), and may also explore the impact of including studies with high levels of missing data.

RESULTS

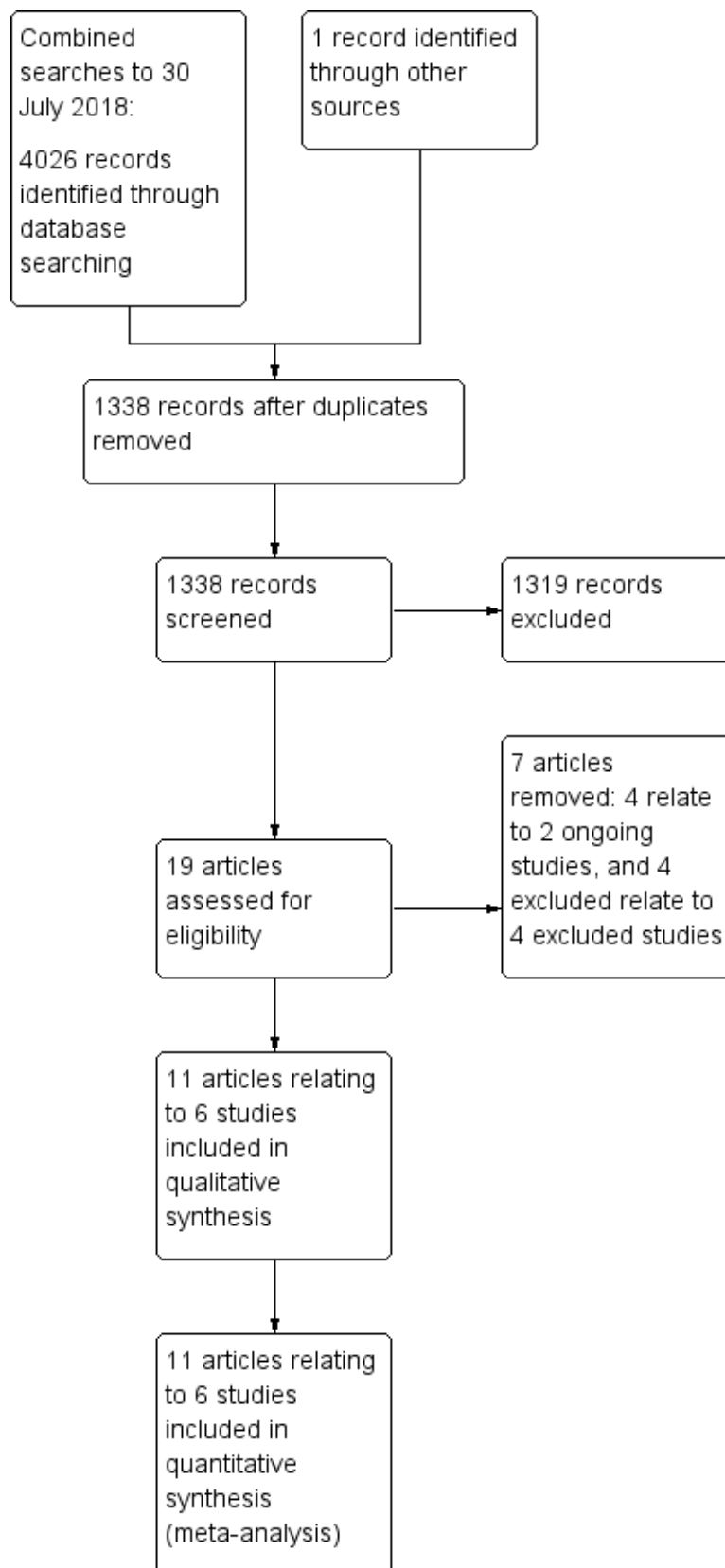
Description of studies

Results of the search

Combined searches to 30 July 2018

When the original search for the 2015 review (894 records) was combined with the 2016 (1369 records) and 2018 search (1763 records) for this update, a total of 4026 records was retrieved. After removal of duplicates, the 2015 search yielded 894 records, the 2016 search yielded a further 354 records, and the 2018 search another 89 records, making a total of 1337 records from these three searches. We identified one additional article from an internet search ([Metha 2015](#)), which brought the total to 1338 records. We discarded 1319 of the records, as the studies they described did not meet the criteria for inclusion. We assessed the full text of the 19 remaining articles for eligibility; we discarded four articles that concerned two ongoing studies (see [Characteristics of ongoing studies](#)), and excluded four articles that reported four studies that did not meet our inclusion criteria (see [Excluded studies](#)). We included the remaining 11 articles (relating to six studies) in the review as these investigated iron therapy as an intervention without the concomitant administration of another therapy ([Edwards 2009](#); [Froessler 2016](#); [Keeler 2017](#); [Kim 2009](#); [Lidder 2007](#); [Serrano-Trenas 2011](#)), see [Figure 3](#).

Figure 3. Study flow diagram for combined searches to 30 July 2018 (fully incorporated into review)



28 November 2019 search

The 2019 top-up search yielded 335 records; after deduplication 242 records remained. These will be examined thoroughly and the results incorporated in the next update of this review. Screening thus far has indicated that 122 records are not relevant, while 116 are worthy of further consideration. Two are additional papers for

a study that is already included in the review ([Keeler 2017](#)); one has been added to the study references, and reference details for the other - a correction - have been appended to those of the relevant paper, thus bringing the total number of references relating to the six included trials to 12. The remaining two records refer to a study that is awaiting classification ([Padmanabhan 2019](#)), see [Figure 4](#).

Figure 4. Study flow diagram for 28 November 2019 top-up searches (not completely incorporated into review)

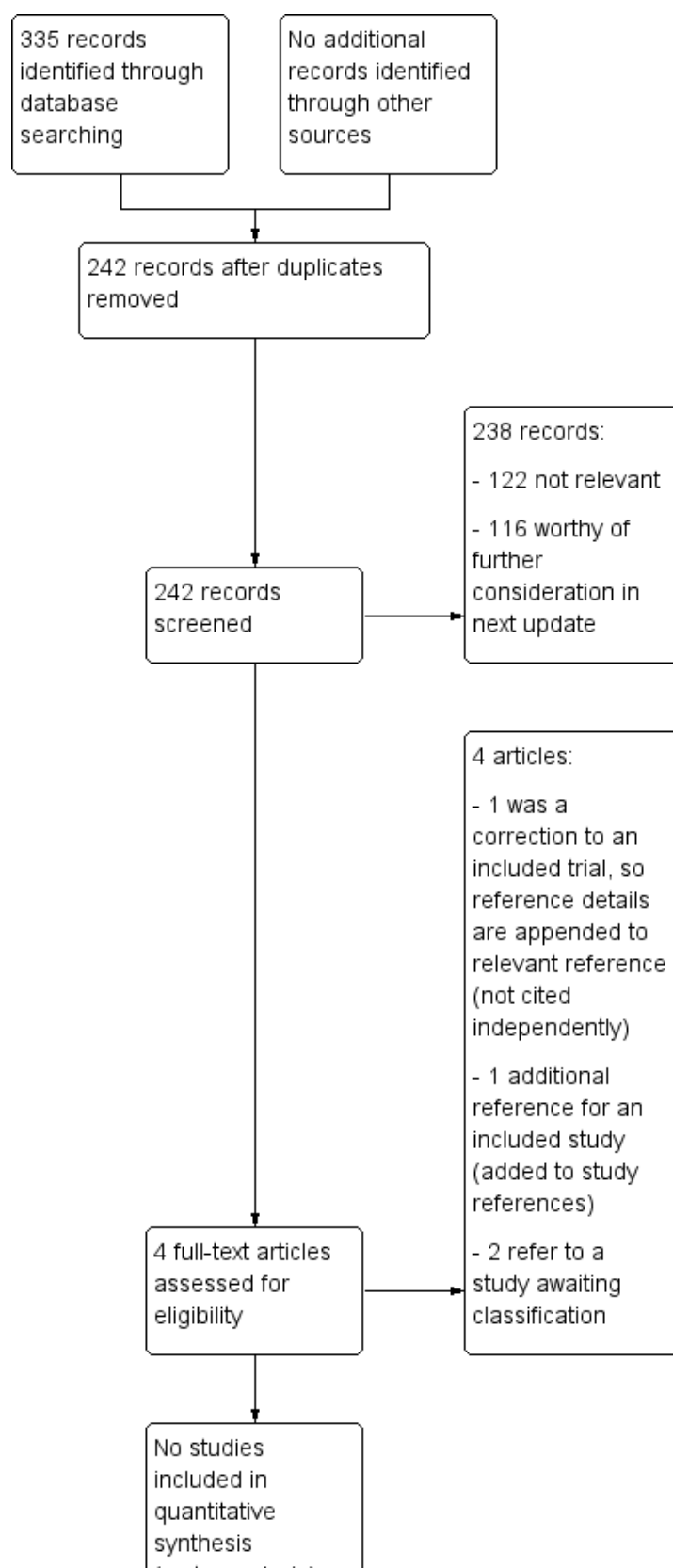


Figure 4. (Continued)

synthesis
(meta-analysis)

Included studies

We found 12 articles relating to six randomised controlled trials (RCTs), with a total of 372 participants, that evaluated the use of preoperative iron therapy to correct anaemia. Four studies were prospectively registered in a clinical trial registry ([Edwards 2009](#); [Froessler 2016](#); [Keeler 2017](#); [Serrano-Trenas 2011](#)), and the two older studies do not appear to have been registered ([Kim 2009](#); [Lidder 2007](#)).

Participants

Three studies were in colorectal surgery ([Edwards 2009](#); [Keeler 2017](#); [Lidder 2007](#)), one in gynaecological surgery ([Kim 2009](#)), one in orthopaedic surgery ([Serrano-Trenas 2011](#)), and one in major abdominal surgery ([Froessler 2016](#)).

Interventions

All six studies detailed the use of iron therapy prior to surgery for preoperative anaemia. One study compared oral iron versus no iron therapy ([Lidder 2007](#)), three studies compared intravenous iron versus placebo or usual care ([Edwards 2009](#); [Froessler 2016](#); [Serrano-Trenas 2011](#)), and two studies compared intravenous iron versus oral iron ([Keeler 2017](#); [Kim 2009](#)).

Interventions and comparisons were either oral or intravenous iron compared to each other or to standard care with or without placebo. [Lidder 2007](#) conducted an open-label, prospective RCT that compared oral ferrous sulphate with no iron therapy. [Edwards 2009](#) compared 600 mg intravenous iron sucrose against placebo a minimum of two weeks before surgery in a prospective, blinded, placebo-controlled randomised trial. [Kim 2009](#) administered either intravenous iron sucrose or oral iron (80 mg/day iron succinylate) in the three weeks preceding surgery. [Serrano-Trenas 2011](#) conducted a prospective RCT that compared standard treatment with 600 mg intravenous iron sucrose. [Froessler 2016](#) gave participants either intravenous ferric carboxymaltose or usual care. Uniquely, in this trial, a preoperative and postoperative dose of intravenous iron were administered; the second postoperatively if blood loss exceeded 100 mL. [Keeler 2017](#) randomised participants to receive either oral ferrous sulphate 200 mg twice a day or intravenous ferric carboxymaltose with dose based upon haemoglobin level and weight.

Outcomes

All studies except [Kim 2009](#) reported the primary outcome of blood transfusion. Studies also reported levels of haemoglobin and ferritin, and morbidity. [Froessler 2016](#) and [Keeler 2017](#) reported quality of life, but the [Keeler 2017](#) study authors did not report these data in time for publication of the present version of this review.

Excluded studies

We excluded four articles relating to four studies: [Metha 2015](#) was excluded because this study was not prospectively registered and was published after 2010. One other study excluded anaemic participants ([Garrido-Martin 2012](#)), while a second had no subgroup

analysis of anaemic participants ([Andrews 1997](#)). The fourth study randomised only non-anaemic participants, and gave all anaemic participants iron ([Crosby 1994](#)). We also identified four articles relating to two ongoing studies which currently have no available data ([NCT01692418](#); [NCT02632760](#)), so could not be included in this iteration of the review.

Risk of bias in included studies

A summary of the review authors' 'Risk of bias' judgements can be found in [Figure 1](#) and [Figure 2](#).

Allocation

All included studies except [Lidder 2007](#) reported allocation using a computer-generated randomisation sequence, so we considered them to be at a low risk of bias for this domain. The method of random sequence allocation was not clearly described in [Lidder 2007](#), so we judged this study to be at an unclear risk of bias for this domain.

We judged all studies except [Lidder 2007](#) and [Serrano-Trenas 2011](#) to be at a low risk of bias for allocation concealment with study methodology describing clear methods for preventing investigators knowledge of assignment (opaque sealed envelopes, investigator blinding), but we considered [Lidder 2007](#) and [Serrano-Trenas 2011](#) to be at an uncertain risk of bias for allocation concealment, as they did not detail how allocation concealment was achieved.

Blinding

Performance bias

One study was placebo-controlled with participants blinded to intervention by means of an opaque sheath over the intravenous giving set and assessed as being at low risk of bias ([Edwards 2009](#)). All other trials were unblinded with either different routes of administration ([Keeler 2017](#); [Kim 2009](#)), or compared to usual care and were assessed as being at unclear risk of bias ([Froessler 2016](#); [Lidder 2007](#); [Serrano-Trenas 2011](#)).

Detection bias

The absence of blinding is less likely to create bias in objective outcome measures, such as changes in haemoglobin and ferritin levels, but could influence subjective assessments, such as quality of life questionnaires; only one study reported quality of life in time to be used in the review, and we assessed it as being at unclear of risk of bias ([Froessler 2016](#)). Blood transfusion, unless administered under a strict transfusion protocol, could potentially be influenced by lack of blinding in these studies. Four studies reported that the clinicians treating participants were blinded to the intervention the participant received and we assessed these as being at low risk of bias ([Edwards 2009](#); [Keeler 2017](#); [Lidder 2007](#); [Serrano-Trenas 2011](#)). One study did not report whether clinicians were blinded ([Kim 2009](#)), and therefore we assessed it as being at unclear risk of bias.

Incomplete outcome data

One study excluded participants with a compliance of less than 80% from the analysis, instead of completing analysis on an intention-to-treat basis, and we considered it to have a high risk of bias (Kim 2009). This is important, especially when considering oral iron therapy, where compliance could be a major factor in the efficacy of the treatment.

One study did not report whether data were analysed on an intention-to-treat basis (Lidder 2007), and we assessed it as being at unclear risk of bias. All other studies included all patient data from participants in their analyses and we assessed them as being at low risk of bias (Froessler 2016; Keeler 2017; Edwards 2009; Serrano-Trenas 2011).

Selective reporting

After comparison of the study register record with the published study reports, we found no evidence of selective reporting in four of the studies included in this review and assessed their risk of bias for this domain as low (Froessler 2016; Keeler 2017; Kim 2009; Lidder 2007). Two studies were not prospectively registered and we assessed them as being at unclear risk for reporting bias (Edwards 2009; Serrano-Trenas 2011).

Other potential sources of bias

One study reported early termination of the study after investigators reported the number of blood transfusions was higher than expected (Froessler 2016). Three independent assessors evaluated interim data and two advised termination due to higher than expected levels of poor outcomes. This interim analysis was conducted independently of the investigators and the data were

blinded. However, the risk of bias is unclear. We judged the risk of bias for this domain to be low for all the other studies.

Effects of interventions

See: [Summary of findings for the main comparison Iron therapy compared to placebo, no treatment or standard care for preoperative anaemia](#); [Summary of findings 2 Intravenous iron therapy compared to oral iron therapy for preoperative anaemia](#)

Comparison 1: iron therapy compared to placebo, no treatment or standard care

Primary outcome: proportion of participants who received a blood transfusion

Four studies measured and reported the proportion of participants who received allogeneic blood transfusions (Edwards 2009; Froessler 2016; Lidder 2007; Serrano-Trenas 2011). Iron therapy produced no clear reduction in the proportion of participants who received a blood transfusion (risk ratio (RR) 1.21, 95% confidence interval (CI) 0.87 to 1.70; $I^2 = 54\%$; 4 studies, 200 participants; moderate-quality evidence; [Analysis 1.1](#)).

Secondary outcomes

Amount of blood transfused per participant (in units)

Four studies measured and reported the number of units of blood transfused in each treatment group (Edwards 2009; Froessler 2016; Lidder 2007; Serrano-Trenas 2011). However, it was not possible to combine the data because they were skewed and one study did not report subset data for the 90 participants who were anaemic at recruitment (Serrano-Trenas 2011). The raw data are given in the table below.

Study	Control	Iron group
Edwards 2009	Median 2 units (interquartile range (IQR) 3 units; n = 9; unspecified number of total units transfused)	Median 0 units (IQR 1 unit; n = 9; unspecified number of total units transfused)
Froessler 2016	Median 0 units (range 0 to 2 units)	Median 0 units (range 0 to 5 units)
Lidder 2007	Median 2.5 units (range 0 to 11 units; n = 14; 39 units transfused in total)	Median 1 unit (range 0 to 2 units; n = 6; 6 units transfused in total)
Serrano-Trenas 2011	Mean 0.87 units (standard deviation (SD) 1.21 units; n = 100 (50 anaemic))	Mean 0.76 units (SD 1.16 units; n = 100 (40 anaemic))

Postoperative mortality in the short term (within 30 days) and long term (from 31 days up to one year)

Two studies did not measure or report mortality (38 participants) (Edwards 2009; Lidder 2007). Two studies measured and reported no clear difference in short-term mortality (162 participants) (Froessler 2016; Serrano-Trenas 2011). In the former study, one death occurred in the intervention group and none in the control; in the latter, 10 participants died in the intervention arm and 11 in the control. As the former study was terminated early, the time periods for these data may not be directly comparable. No studies measured or reported long-term mortality.

Postoperative morbidity (including infections and adverse events)

Two studies did not measure or report postoperative morbidity (38 participants) (Edwards 2009; Lidder 2007). Two studies measured and reported no difference in morbidity (162 participants) (Froessler 2016; Serrano-Trenas 2011). Froessler 2016 reported three minor adverse events: headache, light-headedness and back pain (72 participants). Serrano-Trenas 2011 also reported three minor adverse events: one skin rash and two participants with general discomfort (90 participants). No serious adverse events were reported in any study.

Any validated measure of quality of life

[Froessler 2016](#) reported no clear difference in quality of life scores between groups four weeks after intervention (90 participants), measured using the 36-item Short Form Survey (SF-36) ([Analysis 1.2](#)) ([Ware 1992](#)). The other studies within this comparison did not measure quality of life.

Haematologic parameters measured pretreatment, preoperatively but post-treatment, and postoperatively

Haemoglobin level

Both [Lidder 2007](#) and [Serrano-Trenas 2011](#) collected data on this outcome at two time points, pretreatment and preoperatively post-treatment, but the data were not reported separately for the anaemic participants.

[Edwards 2009](#) and [Froessler 2016](#) reported haemoglobin levels for the 83 anaemic participants at the end of preoperative treatment, when there was no difference in haemoglobin levels between the control and intervention groups (mean difference (MD) 0.63 g/dL, 95% CI -0.07 to 1.34; $I^2 = 41\%$; 2 studies, 83 participants; low-quality evidence; [Analysis 1.3](#)).

Postoperatively, there was no clear difference between haemoglobin levels in the two groups (MD 0.17 g/dL, 95% CI -0.29 to 0.63; $I^2 = 78\%$; 2 studies, 86 participants; low-quality evidence; [Analysis 1.4](#)).

Haematocrit level

The [Edwards 2009](#) study collected data on haematocrit levels pretreatment, at the end of treatment preoperatively, and after treatment postoperatively, but no standard deviation values were reported and so it was not possible to analyse the data.

Ferritin level

The [Lidder 2007](#) and [Serrano-Trenas 2011](#) studies did not report ferritin data separately for anaemic participants.

The [Edwards 2009](#) study collected data on ferritin levels pretreatment, at the end of treatment preoperatively, and after treatment postoperatively, but no standard deviation values were reported and so it was not possible to analyse the data.

Only [Froessler 2016](#) reported an increase in ferritin at four weeks with intravenous iron therapy (MD 149.00, 95% CI 25.84 to 272.16; 1 study, 63 participants; [Analysis 1.5](#)). This is clinically important evidence of iron repletion.

Reticulocyte count

The [Lidder 2007](#) study authors performed reticulocyte counts at two time points, pretreatment and preoperatively post-treatment, but the data were not reported separately for the 20 anaemic participants. The [Edwards 2009](#), [Serrano-Trenas 2011](#) and [Froessler 2016](#) studies did not report reticulocyte count.

Comparison 2: intravenous iron therapy compared to oral iron therapy

Two studies compared intravenous iron therapy to oral iron therapy, [Kim 2009](#) and [Keeler 2017](#) (172 participants).

Primary outcome: proportion of participants who received a blood transfusion

The [Kim 2009](#) study did not measure this outcome. The [Keeler 2017](#) study (116 participants) reported no difference in blood transfusions between the oral and intravenous iron groups overall ([Analysis 2.1](#)).

Secondary outcomes

Amount of blood transfused per participant (in units)

The [Kim 2009](#) study did not measure this outcome. [Keeler 2017](#) (116 participants) reported no difference in the amount of blood transfused ([Analysis 2.2](#)).

Postoperative mortality in the short term (within 30 days) and long term (from 31 days up to one year)

The [Kim 2009](#) study did not measure mortality. [Keeler 2017](#) (116 participants) did not report 30-day mortality, but did report 90-day mortality, for which there was no clear difference between the intervention groups (six deaths in the oral iron group, eight in the intravenous group).

Postoperative morbidity (including infections and adverse events)

There was no difference in the grade or risk of all complications, or infective complications, between interventions in the [Keeler 2017](#) study (116 participants).

The [Kim 2009](#) study reported no severe adverse events, though minor adverse events were observed in each group. These included two cases of myalgia and one case of injection pain in the intravenous iron group, and one report of nausea and one of dyspepsia in the oral iron group (56 participants).

[Keeler 2017](#) reported one serious adverse event, which was a rash that followed administration of intravenous iron, which was treated with an oral antihistamine. Minor adverse events were observed in both groups, most commonly headaches in the intravenous iron group, and two participants experienced dyspepsia and constipation in the oral iron group (116 participants).

Any validated measure of quality of life

The [Kim 2009](#) study did not measure this outcome. The [Keeler 2017](#) study authors did measure quality of life but the data were not reported in time for publication of the present version of this review.

Haematologic parameters measured pretreatment, preoperatively but post-treatment, and postoperatively

Haemoglobin level

The [Kim 2009](#) and [Keeler 2017](#) studies reported haemoglobin levels pretreatment, when there was no difference between the control and intervention groups.

Both the [Kim 2009](#) and [Keeler 2017](#) studies measured haemoglobin levels preoperatively post-treatment. Haemoglobin levels were higher in the intravenous iron therapy group than the oral iron therapy group (MD 1.23 g/dL, 95% CI 0.80 to 1.65; $I^2 = 79\%$; 2 studies, 172 participants; low-quality evidence; [Analysis 2.3](#)).

These results are despite [Kim 2009](#) only analysing those participants with more than 80% compliance with oral iron therapy,

and higher than expected compliance with oral iron therapy seen in the [Keeler 2017](#) study.

Haematocrit level

The [Kim 2009](#) and [Keeler 2017](#) studies did not measure this outcome.

Ferritin level

The [Kim 2009](#) and [Keeler 2017](#) studies reported ferritin levels pretreatment, and there was no difference between the control and intervention groups (MD 6.59 ng/mL, 95% CI -11.75 to 24.93; $I^2 = 20\%$; 2 studies, 151 participants; [Analysis 2.4](#)). The results from these studies have wide standard deviations as a result of small sample sizes and very large differences in ferritin levels that ranged from under 30 ng/mL for iron deficiency to over 1000 ng/mL in participants who were iron replete.

The [Kim 2009](#) and [Keeler 2017](#) studies reported ferritin levels preoperatively post-treatment. Ferritin levels were higher in the intravenous iron therapy group than the oral iron therapy group (MD 395.03 ng/mL, 95% CI 227.72 to 562.35; $I^2 = 69\%$; 2 studies, 151 participants; low-quality evidence; [Analysis 2.5](#)).

Reticulocyte count

The [Kim 2009](#) and [Keeler 2017](#) studies did not measure this outcome.

DISCUSSION

Summary of main results

We identified six prospective, randomised controlled trials (RCTs), involving a total of 372 participants, that evaluated preoperative iron therapy to correct anaemia. Three studies were in colorectal surgery ([Edwards 2009](#); [Keeler 2017](#); [Lidder 2007](#)), one in gynaecological surgery ([Kim 2009](#)), one in orthopaedic surgery ([Serrano-Trenas 2011](#)), and one in major abdominal surgery ([Froessler 2016](#)). Five trials reported the primary outcome (proportion of participants who received allogeneic blood transfusions) for 316 people (200 iron versus standard care or placebo, 116 oral iron versus intravenous iron). Meta-analysis of iron therapy versus placebo, no treatment or standard care showed no reduction in the proportion of participants who received a blood transfusion (risk ratio (RR) 1.21, 95% confidence interval (CI) 0.87 to 1.70; $I^2 = 54\%$; 4 studies, 200 participants; moderate-quality evidence; [Analysis 1.1](#)). Only one study reported transfusion after oral iron or intravenous iron and reported no difference in transfusions ([Keeler 2017](#)). The total number of participants is far smaller than the 891 participants our information size calculation indicated would be necessary to detect a difference.

For the secondary outcomes, [Edwards 2009](#), [Kim 2009](#), [Keeler 2017](#) and [Froessler 2016](#) reported change in haemoglobin level for the anaemic participants specifically. No clear difference in haemoglobin at the end of preoperative treatment was seen with iron therapy compared to placebo or standard care (mean difference (MD) 0.63 g/dL, 95% CI -0.07 to 1.34; $I^2 = 41\%$; 2 studies, 83 participants; low-quality evidence; [Analysis 1.3](#)). There was an increase in haemoglobin with intravenous iron at the end of treatment preoperatively (MD 1.23 g/dL, 95% CI 0.80 to 1.65; $I^2 = 79\%$; 2 studies, 172 participants; low-quality evidence; [Analysis 2.3](#)), however, the [Kim 2009](#) study authors possibly biased their results

through the exclusion of participants who had a less than 80% compliance with treatment.

Ferritin levels were increased by intravenous iron, both when compared to standard care ([Froessler 2016](#)), and compared to oral iron (MD 395.03 ng/mL, 95% CI 227.72 to 562.35; $I^2 = 69\%$; 2 studies, 151 participants; low-quality evidence; [Analysis 2.5](#); [Keeler 2017](#); [Kim 2009](#)).

Other secondary outcomes including quality of life, short-term mortality and postoperative morbidity were not measured or reported in most studies, and where they were there were no clear differences between interventions.

Overall completeness and applicability of evidence

Evidence regarding iron therapy for preoperative anaemia is limited currently, with data available only from six RCTs, three of which had very small sample sizes. Furthermore, the 372 participants available for analysis of the primary outcome constitute only 45% of the 819 participants recommended by the information size calculation, which prevents us from reaching reliable conclusions regarding the effects of iron therapy given preoperatively. These studies are also limited in their generalisability, as only three surgical specialities are represented, albeit specialities where anaemia and blood loss are common. Thus far, no studies have examined cost-effectiveness.

Two ongoing studies in major open abdominal surgery, the PREVENTT trial (500 participants), and in cardiac surgery, the ITACS trial (1000 participants), will substantially increase the amount of available data to analyse, and will include data on safety, e.g. risk of infections, quality of life and cost-effectiveness.

Quality of the evidence

This update from the previous Cochrane Review, [Ng 2015b](#), has doubled the number of included studies from three to six, and increased the number of participants from 114 to 372. The three more recent studies have been larger and better designed, and reported morbidity and mortality fully, and two reported quality of life (though results from [Keeler 2017](#) were not reported in time for publication of the present version of this review). However, the total of 372 participants in our analysis falls far short of the 819 required by our information size calculation to detect a 30% reduction in blood transfusions. The GRADE assessment of quality for the primary outcome measure, proportion of participants who needed a blood transfusion, was moderate quality due to low numbers of participants. We assessed all other outcomes as low quality due to small numbers of participants and the exclusion of non-compliant participants in one trial ([Kim 2009](#)). In addition, the [Kim 2009](#) study made important omissions by not recording blood transfusions and quality of life outcomes. It also excluded data in the final analysis from participants whose compliance was less than 80%, acknowledging that compliance is a major factor in the efficacy of oral iron therapy, but, therefore, not reflecting the reality that many patients do not adhere to oral iron because of side effects.

[Edwards 2009](#), [Lidder 2007](#) and [Serrano-Trenas 2011](#) did not exclude non-anaemic participants, or assess for iron deficiency. While they included a subgroup analysis of anaemic participants, they did not report all data for this anaemic group, and these studies were not powered to show a difference in the group

of participants that might require iron to correct their anaemia, namely those with iron deficiency anaemia. As a result these studies have even fewer participants with which to determine the true effect of iron therapy.

Potential biases in the review process

BK, ON, JS, MB and AA are authors of one of the included trials, [Keeler 2017](#). AM independently extracted data from [Keeler 2017](#) because he was not involved with the study. The Cochrane Funding Arbiter's panel recommended that a new, unconflicted author should repeat the data extraction and assessment of risk of bias. This author, HA, independently checked all data extraction, 'Risk of bias' tables and conclusions, including [Keeler 2017](#), to ensure the data had been extracted and reported accurately.

Agreements and disagreements with other studies or reviews

The six RCTs presented here fail to support the conclusions of observational and case-control studies that have demonstrated that iron therapy reduces allogeneic blood transfusion and improves preoperative haemoglobin levels. These include studies from colorectal surgery ([Okuyama 2005](#); [Quinn 2010](#)), orthopaedics ([Cuenca 2004](#); [Cuenca 2005](#); [Munoz 2014](#); [Theusinger 2007](#)), and gynaecological surgery ([Breyman 2008](#)). These findings also contradict the findings of a much larger and broader systematic review of 72 studies that included 10,605 participants and examined anaemia more generally, including conditions other than preoperative anaemia ([Litton 2013](#)). In the [Litton 2013](#) review, meta-analysis showed intravenous iron to be associated with an increase in haemoglobin (standard MD 6.5 g/L, 95% CI 5.1 g/L to 7.9 g/L) and a reduced risk of blood transfusion (RR 0.74, 95% CI 0.62 to 0.88). Our results however, may be a reflection of the small sample sizes in the six included studies and the ability to detect a difference with so few data.

AUTHORS' CONCLUSIONS

Implications for practice

Preoperative anaemia is associated with fatigue, poorer quality of life, increased blood transfusions and an increased risk of postoperative morbidity and mortality. The most common cause

of anaemia is iron deficiency. Based on the current evidence we cannot conclude that iron therapy improves preoperative anaemia, or reduces the number of patients who receive allogeneic blood transfusions as a result of surgery.

The results for intravenous iron therapy are consistent with a greater increase in haemoglobin and ferritin levels when compared to oral iron, but provide low-quality evidence. However, these conclusions are based on six studies with a total number of participants well below the number we calculate is required to be conclusive. Further research is very likely to change the results.

Implications for research

Higher quality studies are required to determine the efficacy of iron therapy for the treatment of preoperative anaemia. Ideally these should be adequately powered, large, multicentre trials across surgical specialities. They should report data for anaemic patients separately or, ideally, include only anaemic patients. They should assess for aetiology of the anaemia treated, including anaemia of chronic disease and true iron deficiency anaemia. Outcome measurements should include some measure of quality of life, postoperative complications, and morbidity and mortality, in addition to the haematological parameters and frequency of allogeneic blood transfusion reported in most current studies. Researchers should include information about side effects and harms from the intervention. It will be important for these studies to include strict transfusion guidelines and definitions of iron deficiency and anaemia, such as those defined in the international consensus statement on perioperative anaemia and iron deficiency ([Munoz 2017](#)).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Edwards 2009

Methods	Blinded, randomised, placebo-controlled trial
Participants	Preoperative patients undergoing surgery for colorectal cancer (n = 60; note only 18 participants were anaemic)
Interventions	Iron therapy group: 2 doses of IV iron sucrose 300 mg in 250 mL 0.9% saline (total 600 mg), a minimum of 2 weeks before surgery

Edwards 2009 (Continued)

Control group: 2 doses of 250 mL IV placebo (0.9% saline)

Outcomes	Transfusion rates Amount of blood transfused Recruitment and admission haemoglobin
Notes	<p>Study had only 9 anaemic participants in each arm.</p> <p>Authors were contacted by email for subanalysis data but did not respond.</p> <p>This study was prospectively registered through the UK Medicines and Healthcare products Regulatory Agency; EU Clinical Trial Registration Number: 2005-003608-13 UK</p> <p>Ethical Committee Approval was granted from the Cornwall and Plymouth Research Ethics Committee on 26 August 2005.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "allocated to either the treatment (iron) group or a placebo group, based on a computer-generated randomisation sequence provided by the Research and Development Support Unit. To ensure equal numbers of anaemic patients in each treatment group, randomisation was stratified according to pre-recruitment Hb status: normal (Hb level at least 13.5 g/dL in males and 12.5 g/dL in females), anaemic, or unknown (no test within 2 months of recruitment). Block randomisation was used to ensure similar numbers in each group for each subset."
Allocation concealment (selection bias)	Low risk	Quote: "Allocation codes were sealed in sequentially numbered opaque envelopes which were secured within a locked store room in a dedicated research unit."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Although the investigator administering the infusion was not blinded to the treatment group, this was concealed from the patient by using an opaque sheath to cover the drug-giving set."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The chief investigator and clinicians involved in perioperative care also remained blinded to the treatment group for the duration of the trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: it appears there was no loss to follow-up among people with anaemia
Selective reporting (reporting bias)	Unclear risk	Comment: none identified
Other bias	Low risk	Comment: none identified

Froessler 2016

Methods	Randomised controlled trial of IV iron versus control (usual care)
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Froessler 2016 (Continued)

Participants	Adult participants with a ferritin level < 300 µg/L, transferrin saturation < 25% and haemoglobin < 120 g/L in women and < 130 g/L in men undergoing major abdominal surgery (n = 72)
Interventions	<p>Iron therapy group: single-dose IV ferric carboxymaltose 1000 mg or a maximum of 15 mg/kg preoperatively (median 8 days before surgery) with a second dose postoperatively of 50 mg per 100 mL of blood loss</p> <p>Control group: usual care</p>
Outcomes	<p>Primary outcome: allogenic blood transfusion</p> <p>Secondary outcomes: haemoglobin, ICU admission, perioperative morbidity, mortality, length of stay, iron status and quality of life (SF36)</p>
Notes	<p>Study was stopped early after interim data analysis showed high rates of red blood cell transfusion.</p> <p>Quote: "The protocol was approved by the study hospital's human research ethics committee and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12611000387921)." p. 42</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization followed a computer-generated number sequence and allocation was conducted by telephone." p. 42
Allocation concealment (selection bias)	Low risk	Quote: "The surgeon performing the operation was informed of patient participation in the study but group allocation was not revealed." p. 42
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Quote: "The surgeon performing the operation was informed of patient participation in the study but group allocation was not revealed"</p> <p>Comment: no blinding of participants reported and no placebo administered. It is unclear whether this would influence blood transfusion administration, and it would be unlikely to change haemoglobin levels, but could be a major influence on quality of life scores.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no report of who collected outcome data and whether they were aware of the intervention to which participants had been allocated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: none identified
Selective reporting (reporting bias)	Low risk	Comment: none identified
Other bias	Unclear risk	Study was stopped early after interim data analysis showed high rates of red blood cell transfusion

Keeler 2017

Methods	Randomised control trial of IV versus oral iron
Participants	Adult participants with haemoglobin < 110 g/L in women and < 120 g/L in men undergoing elective surgery for colorectal adenocarcinoma (n = 116)

Iron therapy for preoperative anaemia (Review)

Keeler 2017 (Continued)

Interventions	<p>Oral iron therapy group: preoperative oral ferrous sulphate 200 mg twice a day</p> <p>IV iron therapy group: preoperative IV ferric carboxymaltose. The dose was calculated on body weight and haemoglobin; a maximum dose of 1000 mg was administered per week and a maximum of 2000 mg during the trial. If participants required 2 doses, the second dose was administered at least 7 days after the first. The median duration of iron therapy was 21 days in each group.</p>
Outcomes	<p>Primary outcome: blood transfusions</p> <p>Secondary outcomes: haemoglobin, transferrin, saturations and ferritin, quality of life</p>
Notes	<p>Inclusion criteria did not include ferritin or transferrin saturations</p> <p>ClinicalTrials.gov Identifier: NCT01701310, EU Clinical Trials Register Number: 2011-002185-21.</p> <p>According to the EU Clinical Trials Register, ethical approval for the study was granted on 5 September 2011 and received regulatory approval from the Medicines and Healthcare products Regulatory Agency on 15 September 2011.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Recruited patients were randomized in a 1:1 fashion via a web-based system using variable block allocation, stratified by patient age and sex"
Allocation concealment (selection bias)	Low risk	Comment: computer-generated random allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: open-label study with no blinding due to the different routes of intervention administration and the "darkening of stool when ingesting oral iron". It is unclear whether this would influence blood transfusion administration, but it would be unlikely to change other quantitative measures, such as haemoglobin, ferritin or transferrin saturations.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcome assessors not blinded to intervention, but unlikely to influence outcome measures
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 4 participants had their operations cancelled, 1 died during anaesthesia and one was deemed inoperable at laparotomy. Participants analysed on an intention-to-treat basis.
Selective reporting (reporting bias)	Low risk	Comment: none identified
Other bias	Low risk	Comment: none identified

Kim 2009

Methods	Open-label, randomised controlled trial
Participants	Anaemic preoperative participants with menorrhagia who were due to undergo surgery (n = 76; note only 56 participants with > 80% compliance are included in the analysis, Hb < 90 g/L)
Interventions	Oral iron therapy group: preoperative oral iron succinylate (dose 80 mg per day for 3 weeks preceding surgery)

Iron therapy for preoperative anaemia (Review)

Kim 2009 (Continued)

IV iron therapy group: preoperative IV iron sucrose (dose according to Ganzoni's formula for cumulative iron deficit) 3 times a week, beginning 3 weeks before surgery

Outcomes	Recruitment and admission haemoglobin	
Notes	The study took place between December 2005 and January 2007.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomisation table ... [to] randomly assign patients."
Allocation concealment (selection bias)	Low risk	Quote: "Group allocation was determined by one of the authors not directly involved in patient care."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: open-label study, no blinding, but unlikely to influence the change in haemoglobin
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no blinding, objective measurement of haemoglobin unlikely to be influenced, but transfusions potentially influenced
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Participants who had > 80% compliance were included in the analysis" Comment: not analysed on intention-to-treat basis; this is important because oral iron reportedly has poor tolerance, and therefore poor compliance.
Selective reporting (reporting bias)	Low risk	Comment: none identified
Other bias	Low risk	Comment: none identified

Lidder 2007

Methods	Open-label randomised controlled trial	
Participants	Preoperative patients undergoing surgery for colorectal cancer (n = 49; note only 20 participants anaemic)	
Interventions	Iron therapy group: preoperative oral ferrous sulphate 200 mg three times a day for 2 weeks before surgery Control group: no iron therapy	
Outcomes	Transfusion rates and amount of blood transfused Pretreatment and preoperative haemoglobin	
Notes	The trial included anaemic and non-anaemic participants. Data were presented for all participants, and anaemic participants.	

Lidder 2007 (Continued)

Quote: "The study received approval from the Plymouth Healthcare Trust Local Research Ethics Committee." p. 418

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: study did not explain how randomisation was achieved
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomised (by telephone to a distant centre)." p. 419
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The clinical team (surgeons, nurses, anaesthetists) were blinded to treatment allocation. It was not possible to use a placebo and blind the patient, as oral iron alters stool colour." p. 419
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The collection of data was performed by a research fellow not involved in the direct care of the patient."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Two patients from each group were deemed unsuitable for resective surgery at admission, two underwent stent insertion and two were referred to the palliative care team." Comment: no incomplete outcome data were reported
Selective reporting (reporting bias)	Low risk	Comment: none identified from the published report. No study protocol is available for bias assessment.
Other bias	Low risk	Comment: none identified

Serrano-Trenas 2011

Methods	Open-label, randomised controlled trial
Participants	Preoperative patients over 65 years of age undergoing hip fracture surgery (n = 200, 90 participants Hb < 120 g/L at baseline)
Interventions	Iron therapy group: preoperative IV iron sucrose 600 mg in 3 doses of 200 mg IV over 48 hours before surgery Control group: standard care
Outcomes	Transfusion rates Amount of blood transfused Haematinics Mortality Infections rate Length of hospital stay

Serrano-Trenas 2011 (Continued)

Notes

Quote: "This trial was funded by the Spanish Ministry of Health and Consumer Affairs, through the Instituto de Salud Carlos III, under Protocol Code EC07/90842, as part of the Biomedical and Health Science Research Promotion Programme for the implementation of noncommercial clinical research projects using drugs intended for human use, within the framework of the National Plan for Scientific Research, Development and Innovation (RI+D+I) for the period 2004-2007. Prior authorization was obtained from the Spanish Agency for Medicines and Health Products, under EudraCT Number 2007-007044-10." p. 97

According to the EU Clinical Trials Register, ethical approval for the study was granted on 11 February 2008 and approval for the study was granted on 4 March 2008.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Opaque sealed envelopes generated from a randomisation list in blocks of 10
Allocation concealment (selection bias)	Unclear risk	Quote: "neither the patient nor the investigator could know which group the subject was assigned to before his or her consent"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Blinding procedures were not used in this trial" Comment: unclear if lack of blinding would influence transfusion practice or other outcomes, but unlikely to influence haemoglobin and haematinics
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinded evaluation of trial data by an independent evaluator"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: data analysed on intention-to-treat basis
Selective reporting (reporting bias)	Unclear risk	Comment: none identified
Other bias	Low risk	Comment: none identified

Abbreviations

h: hour(s)

Hb: haemoglobin

ICU: intensive care unit

IV: intravascular

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Andrews 1997	Not a randomised controlled trial. All anaemic participants given iron therapy with no control arm. Non-anaemic participants were randomised, but since they did not have preoperative anaemia, we excluded this study from the review.
Crosby 1994	Study included all participants, anaemic and non-anaemic, did not stratify results to allow analysis of the subset of participants with preoperative anaemia and randomised only non-anaemic participants giving all anaemic participants iron.

Study	Reason for exclusion
Garrido-Martin 2012	Study specifically excluded people with previous anaemia, therefore no participants in this study had preoperative anaemia.
Metha 2015	Study was not registered prospectively. In order to be eligible for inclusion in the review, all RCTs taking place after 2010 must have been prospectively registered (Roberts 2015).

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Padmanabhan 2019](#)

Methods	Randomised non-blinded, single centre pilot study
Participants	<p>Participants were scheduled for elective cardiac surgery, defined as coronary artery bypass graft and/or open valve surgery, who were anaemic according to the WHO criteria (haemoglobin < 120 g/L for women and < 130 g/L for men).</p> <p>Exclusion criteria: deficiencies in B₁₂ or folic acid; low haemoglobin attributable to haemoglobinopathy; participating in another trial; inability to provide written consent; recognised allergy or other contraindications to IV iron or related products; already receiving IV iron treatment; evidence of significant symptomatic anaemia that would normally require urgent transfusion at the time of assessment; haemoglobin > 90 g/L (9.0 g/dL); blood transfusion between enrolment and admission and pregnancy and/or breastfeeding</p>
Interventions	<p>Oral iron therapy group: 200mg ferrous sulphate twice daily, for 3-8 weeks before elective cardiac surgery</p> <p>IV iron therapy group: ferric carboxymaltose therapy, with dose calculated using a fixed dosing regimen, 3-8 weeks before elective cardiac surgery</p>
Outcomes	<p>Primary outcome: change in haemoglobin concentration before and approximately 3 weeks after iron therapy</p> <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • biomarkers of iron metabolism such as iron, ferritin, transferrin, C-reactive protein, total iron binding capacity and erythropoietin on the day of recruitment and on the day of surgery • transfusion requirements and postoperative complications (acute kidney injury, atrial fibrillation and any infection, such as chest infection, surgical site infection and septicaemia) • patient-related outcomes such as duration of in-hospital stay and quality of life measures, such as those recorded using the modified Short Form-36 (SF-36) version 1 and EUROQOL-5D (EQ-5D) questionnaires.
Notes	"Although commercial funding was received for the study, Vifor did not contribute to the study design or have access to study data" (Padmanabhan 2019 p 450).

Abbreviations

IV: intravenous

WHO: World Health Organization

Characteristics of ongoing studies *[ordered by study ID]*

[NCT01692418](#)

Trial name or title	PREVENTT
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Iron therapy for preoperative anaemia (Review)

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NCT01692418 (Continued)

Methods	Phase III double-blind randomised controlled trial
Participants	500 patients with anaemia (haemoglobin < 120 g/L) undergoing major open abdominal surgery
Interventions	IV ferric carboxymaltose (dose 1000 mg) compared with placebo 10-42 days before major open abdominal surgery
Outcomes	Primary outcome: blood transfusion Secondary outcomes: postoperative recovery, length of hospital stay, health care utilisation and cost analysis
Starting date	January 2014
Contact information	Toby Richards, MD FRCS University College, London, UK
Notes	Estimated study completion date August 2019

NCT02632760

Trial name or title	Intravenous iron for treatment of anaemia before cardiac surgery (ITACS)
Methods	Randomised double-blind, controlled phase IV trial
Participants	1000 patients with anaemia before elective cardiac surgery
Interventions	Preoperative IV ferric carboxymaltose (dose 1000 mg) compared with placebo
Outcomes	Primary outcome: days alive and out of hospital Secondary outcomes: haemoglobin, ICU stay, hospital stay, survival, quality of life and cost-effectiveness
Starting date	15 July 2016
Contact information	Paul S Myles, MD Bayside Health, Melbourne, Victoria, Australia
Notes	Estimated study completion date October 2020

Abbreviations

ICU: intensive care unit

IV: intravenous

DATA AND ANALYSES

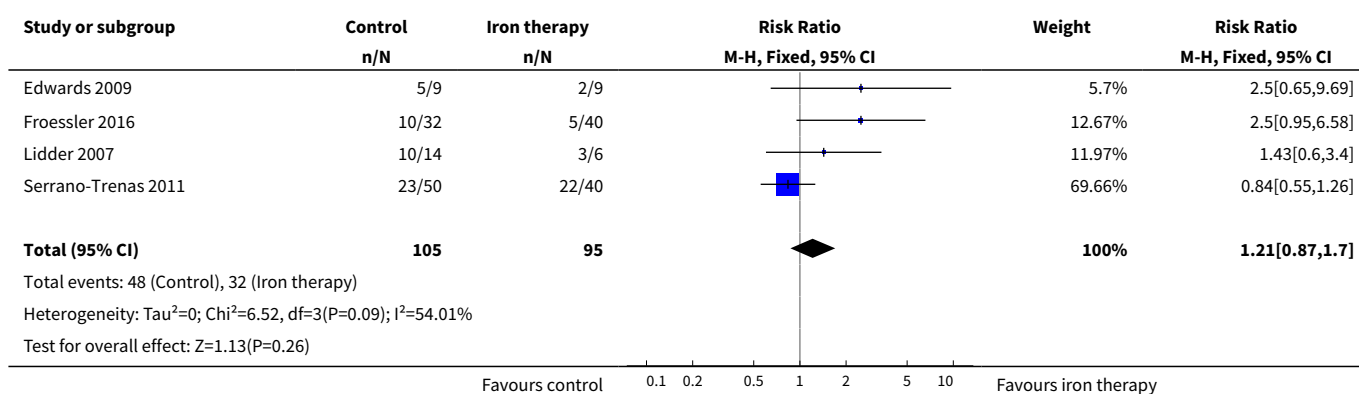
Comparison 1. Iron therapy versus placebo, no treatment or standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants who received a blood transfusion	4	200	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.87, 1.70]

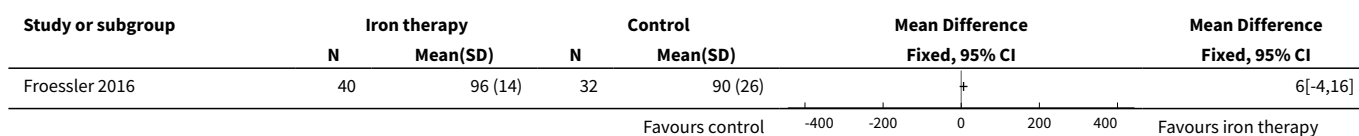
Iron therapy for preoperative anaemia (Review)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Quality of life (SF-36) 4 weeks postoperatively	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Haemoglobin levels preoperatively postintervention (g/dL)	2	83	Mean Difference (IV, Fixed, 95% CI)	0.63 [-0.07, 1.34]
4 Haemoglobin levels postintervention postoperatively (g/dL)	2	86	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.29, 0.63]
5 Ferritin level post-treatment (ng/mL)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

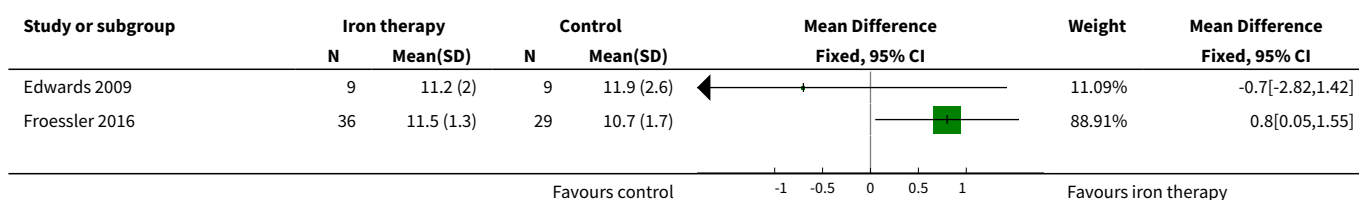
Analysis 1.1. Comparison 1 Iron therapy versus placebo, no treatment or standard care, Outcome 1 Proportion of participants who received a blood transfusion.

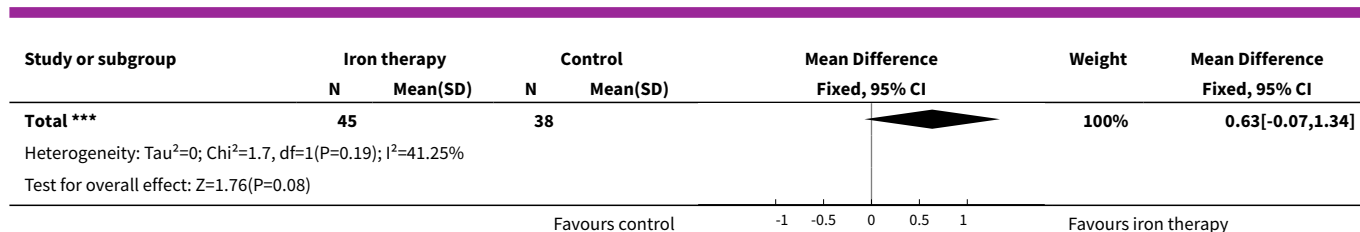


Analysis 1.2. Comparison 1 Iron therapy versus placebo, no treatment or standard care, Outcome 2 Quality of life (SF-36) 4 weeks postoperatively.

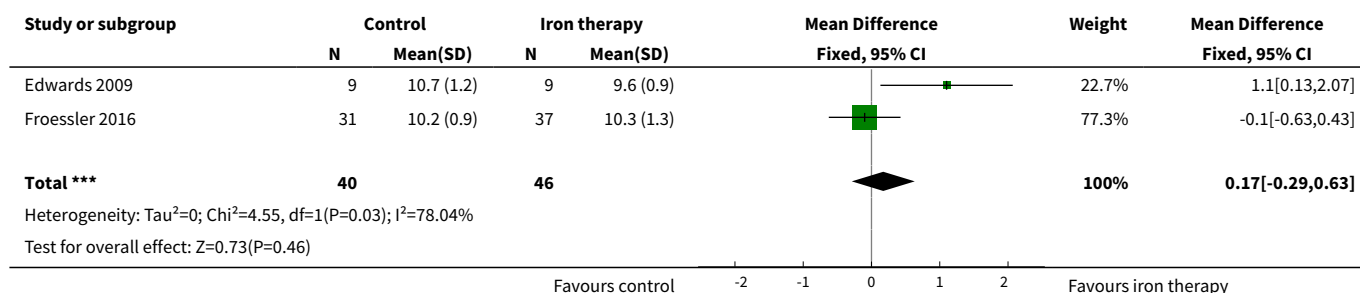


Analysis 1.3. Comparison 1 Iron therapy versus placebo, no treatment or standard care, Outcome 3 Haemoglobin levels preoperatively postintervention (g/dL).

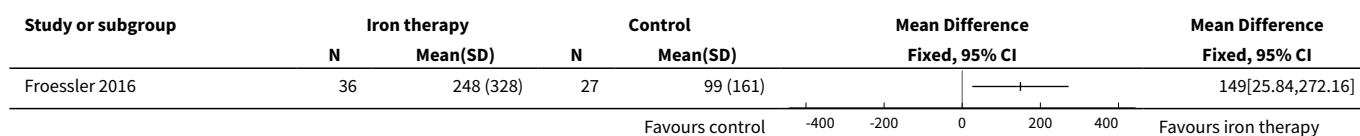




Analysis 1.4. Comparison 1 Iron therapy versus placebo, no treatment or standard care, Outcome 4 Haemoglobin levels postintervention postoperatively (g/dL).



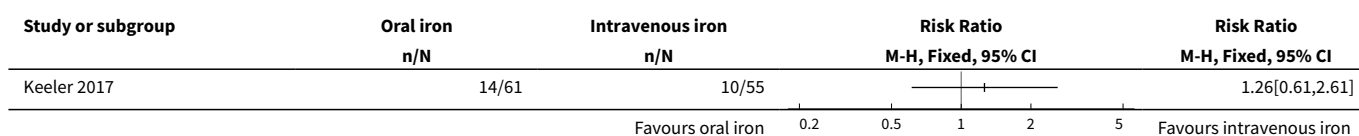
Analysis 1.5. Comparison 1 Iron therapy versus placebo, no treatment or standard care, Outcome 5 Ferritin level post-treatment (ng/mL).



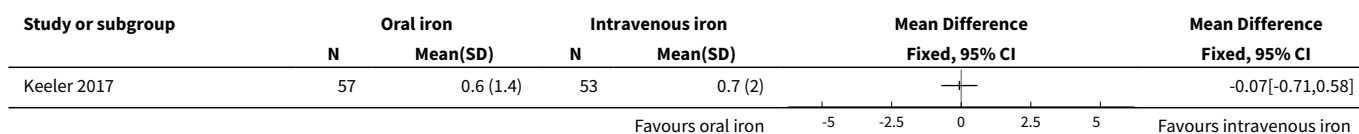
Comparison 2. Intravenous versus oral iron therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants who received a blood transfusion	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Number of units of red blood cells received	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Haemoglobin level preoperatively postintervention (g/dL)	2	172	Mean Difference (IV, Fixed, 95% CI)	1.23 [0.80, 1.65]
4 Ferritin level pretreatment (ng/mL)	2	151	Mean Difference (IV, Fixed, 95% CI)	6.59 [-11.75, 24.93]
5 Ferritin level preoperatively postintervention (ng/mL)	2	151	Mean Difference (IV, Fixed, 95% CI)	395.03 [227.72, 562.35]

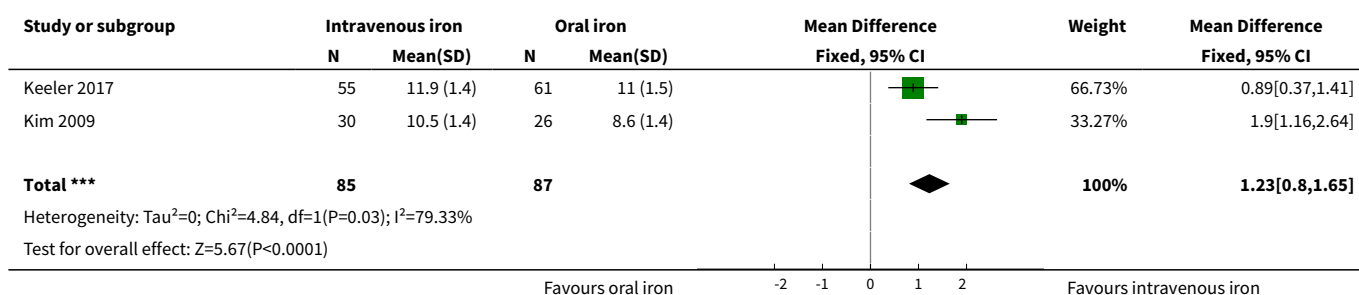
Analysis 2.1. Comparison 2 Intravenous versus oral iron therapy, Outcome 1 Number of participants who received a blood transfusion.



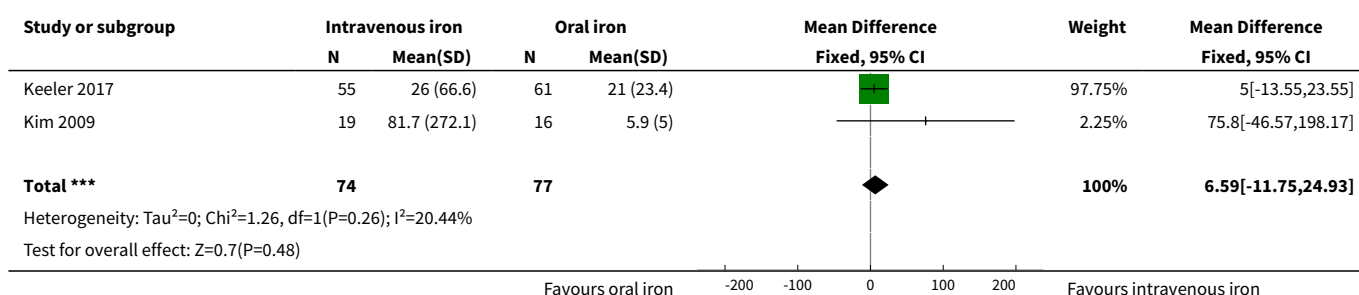
Analysis 2.2. Comparison 2 Intravenous versus oral iron therapy, Outcome 2 Number of units of red blood cells received.



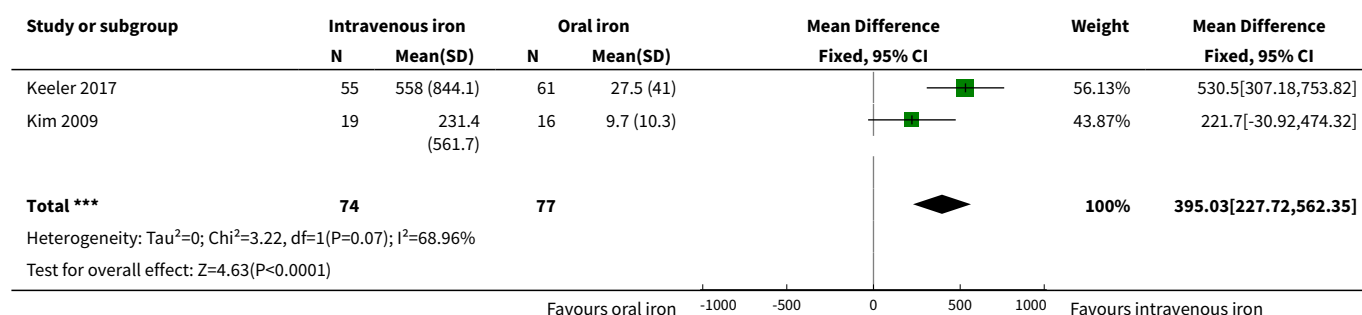
Analysis 2.3. Comparison 2 Intravenous versus oral iron therapy, Outcome 3 Haemoglobin level preoperatively postintervention (g/dL).



Analysis 2.4. Comparison 2 Intravenous versus oral iron therapy, Outcome 4 Ferritin level pretreatment (ng/mL).



Analysis 2.5. Comparison 2 Intravenous versus oral iron therapy, Outcome 5 Ferritin level preoperatively postintervention (ng/mL).



APPENDICES

Appendix 1. Search strategies for 30 July 2018 electronic searches

Cochrane Injuries Group Specialised Register & Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (all years to Issue 10, 2018)

#1 MESH DESCRIPTOR iron EXPLODE ALL TREES
 #2 MeSH descriptor: [Iron Compounds] explode all trees
 #3 iron:TI,AB,KY
 #4 (((ferric OR ferrous):TI,AB,KY
 #5 MeSH descriptor: [Hematinics] explode all trees
 #6 (#1 OR #2 OR #3 OR #4 OR #5)
 #7 MESH DESCRIPTOR preoperative period EXPLODE ALL TREES
 #8 MESH DESCRIPTOR preoperative care
 #9 (((prior OR before) adj3 (surg* OR operat*)):TI,AB,KY
 #10 (preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) next (operat* or procedur* or surgi* or surgu*)):ti,ab,kw
 #11 (#7 OR #8 OR #9 OR #10)
 #12 (#6 AND #11)

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (all years to 30 July 2018)

1. exp Iron/
 2. exp Iron Compounds/
 3. iron.ab,ti,kf.
 4. (ferric or ferrous) .ab,ti,kf.
 5. exp Hematinics/
 6. or/1-5
 7. exp Anemia/
 8. Iron/df [deficiency]
 9. (anaemi* or anemi*).ti,ab,kf.
 10. exp Blood Transfusion/
 11. transfusion.ab.
 12. or/7-11
 13. (preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) adj (operat* or procedur* or surgi* or surgu*)):ti,ab,kf.
 14. ((prior or before) adj3 (surg* or operat*)).ab,ti,kf.
 15. exp Preoperative Period/
 16. Preoperative Care/
 17. or/13-16
 18. (6 and 12 and 17)
 19. (randomi#ed or randomi#ation).ab,ti.
 20. randomized controlled trial.pt.

21. controlled clinical trial.pt.
22. placebo.ab.
23. clinical trials as topic.sh.
24. randomly.ab.
25. trial.ti.
26. Comparative Study/
27. or/19-26
28. (animals not (humans and animals)).sh.
29. 27 not 28
30. (18 and 29)

Ovid EMBASE 1974 to 30 July 2018

1. Iron/
2. Iron Derivative/
3. iron.ab,ti,kf.
4. (ferric or ferrous).ti,ab,kw.
5. exp antianemic agent/
6. or/1-5
7. exp Anemia/
8. (anaemi* or anemi*).ti,ab,kw.
9. exp Blood Transfusion/
10. transfusion.ab.
11. or/7-10
12. (preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) adj (operat* or procedur* or surgu* or surgu*))).ti,ab,kw.
13. ((prior or before) adj3 (surg* or operat*)).ab,ti,kw.
14. exp Preoperative Period/
15. or/12-14
16. (randomi#ed or randomi#ation).ab,ti.
17. randomized controlled trial/
18. (RCT or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or substitut* or treat*))).ab,kw.
19. placebo/
20. placebo.ab.
21. randomly.mp. or "at random".ab.
22. trial.ti.
23. or/16-22
24. exp animal/ not (exp human/ and exp animal/)
25. 23 not 24
26. 6 and 11 and 15 and 25

PubMed (to 30 July 2018)

((((((("Comparative Study"[Publication Type]) OR "Randomized Controlled Trial"[Publication Type]) OR "Controlled Clinical Trial"[Publication Type]) OR (((((((randomized[Title/Abstract]) OR randomised[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract]) OR group[Title/Abstract]))) NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))) AND (((((((("preoperative surgery"[Title/Abstract]) OR "before surgery"[Title/Abstract]) OR "before surgical intervention"[Title/Abstract]) OR "before operation"[Title/Abstract]) OR (("Preoperative Period"[Mesh]) OR "Preoperative Care"[Mesh:noexp]))) AND (((((((iron[Title/Abstract]) OR Ferrous compound*[Title/Abstract]) OR ferric compound*[Title/Abstract]) OR (((("Iron"[Mesh]) OR "Ferric Compounds"[Mesh]) OR "Ferrous Compounds"[Mesh]))))

Web of Science Indexes

SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI (all years to 3 November 2016)

Topic search

- #1 (iron or ferric or ferrous)
- #2 (preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg*)
- #3 (pre-operat* or peri-operati* or pre-procedur* or peri-procedur* or pre-surg* or peri-surg*)
- #4 (anemi* or anaemi* or transfus*)
- #5 (#1 and (#2 or #3) and #4)
- #6 (RCT or random* or placebo)
- #7 (((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*)))

Iron therapy for preoperative anaemia (Review)

#8 (trial)
#9 (#6 or #7 or #8)
#10 (#4 and #9)

ClinicalTrials.gov 30 July 2018

Basic Search: IRON AND (PREOPERATIVE OR PERIOPERATIVE OR PERIPROCEDURAL OR PRE-OPERATIVE OR PERI-OPERATIVE OR PERI-PROCEDURAL)

WHO International Clinical Trials Registry Platform (ICTRP) Search Portal 30 July 2018

Basic Search: ANEMIA AND IRON AND PREOPERATIVE OR ANEMIA AND IRON AND PERIOPERATIVE OR ANEMIA AND IRON AND PERIPROCEDURAL OR ANEMIA AND IRON AND PRE-OPERATIVE OR ANEMIA AND IRON AND PERI-OPERATIVE OR ANEMIA AND IRON AND PERI-PROCEDURAL OR ANAEMIA AND IRON AND PREOPERATIVE OR ANAEMIA AND IRON AND PERIOPERATIVE OR ANAEMIA AND IRON AND PERIPROCEDURAL OR ANAEMIA AND IRON AND PRE-OPERATIVE OR ANAEMIA AND IRON AND PERI-OPERATIVE OR ANAEMIA AND IRON AND PERI-PROCEDURAL

Appendix 2. Search strategies for 28 November 2019 electronic searches

Cochrane Injuries Group Specialised Register & Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library) (all years to 28 November 2019)

#1 MeSH descriptor: [Iron] in all MeSH products
#2 MeSH descriptor: [Iron Compounds] explode all trees
#3 iron:TI,AB,KW
#4 (ferric OR ferrous):TI,AB,KW
#5 MeSH descriptor: [Hematinics] in all MeSH products
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor: [Preoperative Period] explode all trees
#8 MeSH descriptor: [Preoperative Care] explode all trees
#9 ((prior OR before) near/3 (surg* OR operat*)):TI,AB,KW
#10 (preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) next (operat* or procedur* or surgi* or surgu*)):ti,ab,kw
#11 (#7 OR #8 OR #9 OR #10)
#12 (#6 AND #11)

Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (all years to 28 November 2019)

1. exp Iron/
2. exp Iron Compounds/
3. iron.ab,ti,kf.
4. (ferric or ferrous).ab,ti,kf.
5. exp Hematinics/
6. or/1-5
7. exp Anemia/
8. Iron/df [deficiency]
9. (anaemi* or anemi*).ti,ab,kf.
10. exp Blood Transfusion/
11. transfusion.ab.
12. or/7-11
13. (preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) adj (operat* or procedur* or surgi* or surgu*)):ti,ab,kf.
14. ((prior or before) adj3 (surg* or operat*)).ab,ti,kf.
15. exp Preoperative Period/
16. Preoperative Care/
17. or/13-16
18. 6 and 12 and 17
19. (randomi#ed or randomi#ation).ab,ti.
20. randomized controlled trial.pt.
21. controlled clinical trial
22. placebo.ab.
23. clinical trials as topic.sh.
24. randomly.ab.
25. trial.ti.

26. Comparative Study/
27. or/19-26
28. (animals not (humans and animals)).sh.
29. 27 not 28
30. 18 and 29

Ovid EMBASE 1974 to 28 November 2019

1. Iron/
2. Iron Derivative/
3. iron.ab,ti,kw.
4. (ferric or ferrous).ti,ab,kw.
5. exp antianemic agent/
6. or/1-5
7. exp Anemia/
8. (anaemi* or anemi*).ti,ab,kw.
9. exp Blood Transfusion/
10. transfusion.ab.
11. or/7-10
- 12.(preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg* or ((pre or peri) adj (operat* or procedur* or surgi* or surgu*)))ti,ab,kw.
13. ((prior or before) adj3 (surg* or operat*)).ab,ti,kw.
14. exp Preoperative Period/
15. or/12-14
16. (randomi#ed or randomi#ation).ab,ti.
17. randomized controlled trial/
18. (RCT or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or substitut* or treat*))).ab,kw.
19. placebo/
20. placebo.ab.
21. randomly.mp. or "at random".ab.
22. trial.ti.
23. or/16-22
24. exp animal/ not (exp human/ and exp animal/)
25. 23 not 24
26. 6 and 11 and 15 and 25

PubMed (to 28 November 2019)

((((((("Comparative Study"[Publication Type]) OR "Randomized Controlled Trial"[Publication Type]) OR "Controlled Clinical Trial"[Publication Type]) OR (((((((randomized[Title/Abstract]) OR randomised[Title/Abstract]) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR trial[Title/Abstract]) OR groups[Title/Abstract]) OR group[Title/Abstract]))) NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))) AND (((((((("preoperative surgery"[Title/Abstract]) OR "before surgery"[Title/Abstract]) OR "before surgical intervention"[Title/Abstract]) OR "before operation"[Title/Abstract]) OR (("Preoperative Period"[Mesh]) OR "Preoperative Care"[Mesh:noexp]))) AND (((((iron[Title/Abstract]) OR Ferrous compound*[Title/Abstract]) OR ferric compound*[Title/Abstract]) OR (("Iron"[Mesh]) OR "Ferric Compounds"[Mesh]) OR "Ferrous Compounds"[Mesh])))

Web of Science Indexes

SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI (all years to 28 November 2019)

Topic search

- #1 (iron or ferric or ferrous)
- #2 (preoperat* or perioperati* or preprocedur* or periprocedur* or presurg* or perisurg*)
- #3 (pre-operat* or peri-operati* or pre-procedur* or peri-procedur* or pre-surg* or peri-surg*)
- #4 (anemi* or anaemi* or transfus*)
- #5 (#3 OR #2)
- #6 (#4 AND #1)
- #7 #6 and #5
- #8 (RCT or random* or placebo)
- #9 (((singl* OR doubl* OR trebl* OR tripl*) SAME (blind* OR mask*)))
- #10 (trial)
- #11 (#10 or #9 or #8)

Iron therapy for preoperative anaemia (Review)

ClinicalTrials.gov 28 November 2019

Basic search: IRON AND (PREOPERATIVE OR PERIOPERATIVE OR PERIPROCEDURAL OR PRE-OPERATIVE OR PERI-OPERATIVE OR PERI-PROCEDURAL)

WHO International Clinical Trials Registry Platform (ICTRP) Search Portal 28 November 2019

Basic search: ANEMIA AND IRON AND PREOPERATIVE OR ANEMIA AND IRON AND PERIOPERATIVE OR ANEMIA AND IRON AND PERIPROCEDURAL OR ANEMIA AND IRON AND PRE-OPERATIVE OR ANEMIA AND IRON AND PERI-OPERATIVE OR ANEMIA AND IRON AND PERI-PROCEDURAL OR ANAEMIA AND IRON AND PREOPERATIVE OR ANAEMIA AND IRON AND PERIOPERATIVE OR ANAEMIA AND IRON AND PERIPROCEDURAL OR ANAEMIA AND IRON AND PRE-OPERATIVE OR ANAEMIA AND IRON AND PERI-OPERATIVE OR ANAEMIA AND IRON AND PERI-PROCEDURAL

WHAT'S NEW

Date	Event	Description
6 December 2019	New search has been performed	The results from the search run on 30 July 2018 have been incorporated into the review. Three new studies, involving 258 participants, are included in the review. A top-up search was run on 28 November 2019; one additional study is awaiting classification.
6 December 2019	New citation required and conclusions have changed	The results have changed. The authors of the review have changed.

CONTRIBUTIONS OF AUTHORS

AM, BK, AS, JS: main contribution to the study concepts and study design

ON, BK, HA: main contribution to the data acquisition, analysis, interpretation and manuscript preparation

KN: main contribution to statistical support

MB, AA: main contribution to supervision and revision of the manuscript

HA: checked all extracted data, 'Risk of bias' assessments and conclusions

DECLARATIONS OF INTEREST

The lead author, ON, is in breach of Cochrane Commercial policy due to having received honoraria and travel support from Pharmacosmos (Denmark) and Vifor Pharma (Switzerland) within the last three years. The Cochrane Funding Arbiter's panel recommended that:

- a new, unconflicted author should check the data extraction and risk of bias tables;
- a member of the editorial group should check that this has been done;
- the final published version of the review should include a clear statement that the lead author is in breach of Cochrane Commercial policy together with a description of the Funding Arbiter Panel's recommendation and the actions taken.

A new unconflicted author, HA, has independently checked all data extraction, 'Risk of bias' tables and conclusions, including [Keeler 2017](#), to ensure there was no bias in the review findings, and has agreed that the reporting of the review was valid. Elizabeth Royle (Editor/Managing Editor for the Cochrane Injuries Group) also checked the data. The clear statement relating to the Funding Arbiter Panel's recommendation is quoted above.

MB's research department has received grant support from Syner-Med (UK) and Vifor Pharma (Switzerland). MB has received honoraria and travel support for consulting or lecturing from Vifor Pharma and Merck Sharp and Dohme Limited (UK).

AA's research department has received grant support from Syner-Med (UK), Vifor Pharma (Switzerland) and Pharmacosmos (Denmark). AA has received honoraria and travel support for consulting or lecturing from Ethicon (UK), Johnson & Johnson (UK), Olympus (UK) and Vifor Pharma (Switzerland).

BK, ON, JS, MB and AA are authors of one of the included trials, [Keeler 2017](#), but AM independently extracted data from [Keeler 2017](#) to avoid bias.

HA, KN, AS and AM have no interests to declare.

Iron therapy for preoperative anaemia (Review)

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SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), Department of Health, UK.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the previous version of this review we assessed short-term mortality as death within 30 days of surgery, and long-term mortality as death a year or more after surgery ([Ng 2015b](#)). For this 2019 update of the review, we have adjusted long-term mortality to death from 31 days up to one year after surgery.

NOTES

In the next update of the review we will include side effects from the intervention as an additional primary outcome. We will use trial sequential analysis to assess the statistical validity of the analyses. We will conduct a health economic evaluation based upon cost-utility and cost-effectiveness.

INDEX TERMS

Medical Subject Headings (MeSH)

*Preoperative Care; Anemia, Iron-Deficiency [prevention & control] [*therapy]; Iron, Dietary [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Humans